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Internal Carotid Artery Stenosis: Rate of Progression

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Objectives: *to assess the incidence and the rate of progression of internal carotid artery (ICA) stenosis and to determine the related risk factors.*
Design: *open prospective study.*
Materials and methods: *between 1988–1997, 442 carotid arteries with various degrees of stenosis were followed using colour duplex ultrasonography every 6 months. Of these arteries, 290 (66%) were asymptomatic, 62 (14%) had caused transient ischaemic attack and 90 (20%) a stroke. In 145 cases (33%), there was concomitant coronary artery disease (CAD), in 134 (30%) diabetes mellitus, in 248 (56%) hypertension, in 139 (31%) hypercholesterolaemia and in 370 (84%) history of smoking. Of the plaques, 44 (10%) were uniformly echolucent, 19 (4%) haemorrhagic, 136 (31%) predominantly echolucent, 146 (33%) predominantly echogenic and 97 (22%) uniformly echogenic.*
Results: *significant progression of stenosis occurred in 82 cases (19%). The mean progression rate in these cases was 15% annually (range: 5–50%). There was no statistically significant correlation between the progression of the ICA stenosis and initial neurological status, age, gender, diabetes mellitus, hypertension, hypercholesterolaemia and smoking habit. Stenosis progression was correlated only with CAD and the ultrasonographic characteristics of the plaques. Patients with CAD as well as those with uniformly echolucent plaques presented a higher incidence and rate of stenosis progression* ($p<0.05$).
Conclusions: *progression of internal carotid artery stenosis occurred in 19% of cases. The mean progression rate in these patients was 15% annually and was correlated with CAD and the ultrasonographic characteristics of the plaque.*

Key Words: Carotid artery stenosis; Ultrasonography; Natural history; Rate of progression; Risk factors.

Introduction

Recent randomised trials of medical versus surgical management of carotid disease have outlined specific operative indications relating to the patient's symptoms and the severity of stenosis.[1–3] The long-term benefits of carotid endarterectomy are realised in symptomatic patients with carotid artery stenosis of >70% and in asymptomatic patients with carotid artery stenosis of >60%. Among patients undergoing colour duplex examination, few will meet these criteria for endarterectomy. The majority will have mild atherosclerotic lesions and will only be considered for further follow-up. Several questions will arise in this group of patients, concerning the risk of disease progression, the rate of progression and the identification of groups of patients being at greater risk for progression of stenosis. Such an identification could be based either on patient-specific or duplex-specific criteria.

The aim of our study was to assess the incidence and the rate of progression of internal carotid stenosis and to determine the related risk factors affecting the natural history of the disease. Special emphasis was laid on the ultrasonographic characteristics of the plaques, in order to assess the value of duplex ultrasonography in predicting the progression of internal carotid artery stenosis.

Patients and Methods

Over a 10-year period from 1988 to 1997, 332 patients with internal carotid artery (ICA) stenosis were followed using colour duplex ultrasonography every 6 months. Eligibility for entering this study required asymptomatic stenosis of any degree or symptomatic stenosis <50% at the time of entry. Arteries without stenosis or with total occlusion as well as arteries operated upon were excluded, leading to a total of 442 carotid arteries being included in our study.

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At the time of the initial scan a complete medical history was taken and the following risk factors recorded: age, gender, coronary artery disease (angina pectoris, myocardial infarction, coronary artery bypass grafting procedure or percutaneous transluminal coronary angioplasty), diabetes mellitus (patients on diet, oral hypoglycaemic agents or insulin, or with fasting glucose levels >7 mmol/l), hypertension (blood pressure greater than 160 mmHg systolic and/or 95 mmHg diastolic), hypercholesterolaemia (total cholesterol >5.2 mmol/l) and smoking habit (current or quit).

Among the arteries studied, 290 (66%) were asymptomatic, 62 (14%) had caused transient ischaemic attack (TIA) and 90 (20%) stroke. Of these arteries, 320 belonged to men (76%) and 122 to women (24%). At the time of the initial scan, mean age of the patients was 66.8 years (range: 40–85 years) and the mean stenosis 45% (range: 30–95%). Initial stenosis was $\geq$50% in 136 (31%) arteries and <50% in 306 (69%). Diabetes mellitus was present in 134 cases (30%), hypertension in 248 (56%), coronary artery disease in 145 (33%), hypercholesterolaemia in 139 (31%) and history of smoking in 370 (84%).

The ultrasonographic characteristics of the plaques were also recorded, with the plaques being divided into five categories: 44 (10%) were uniformly echolucent (type I), 19 (4%) haemorrhagic, 136 (31%) predominantly echolucent (type II), 146 (33%) predominantly echogenic (III) and 97 (22%) echogenic (IV). The presence of intraplaque haemorrhage was suggested by a hypo-anechogenic stria separating the intimal plaque from the media–adventitia complex. Only plaques, which undoubtedly fulfilled this criterion were characterised as "haemorrhagic". All patients were followed with a colour duplex scan every 6 months. An ATL Interspec Apogee scanner with a 7.5 MHz probe was used (Advanced Technologies Laboratories, Bothell, Washington, U.S.A.) Eight categories of carotid stenosis (expressed as the percentage decrease in artery diameter) were defined based on the B-mode image and on velocity criteria: ICA peak systolic velocity (PSV), end-diastolic velocity (EDV) and ICA/CCA (common carotid artery) PSV ratio (Table 1). Patients were classified according to the highest degree of stenosis identified (maximum stenosis).

The main outcome studied was progression of the degree of ICA stenosis, as defined by any change to a higher category of carotid stenosis. The rate of progression was estimated using the mean value of each category. Follow-up was terminated at the date of death, stroke, total occlusion or carotid endarterectomy. The incidence and the rate of ICA stenosis progression were analysed in association with the recorded risk factors. Statistical analysis was performed using the one way analysis of variance, the χ^2 test and the Student's *t*-test (SPSS/PC+, version 8.0). For results confirming the *a priori* hypothesis of the study, a *p*-value <0.05 was considered significant. For all other analyses, the Bonferroni method was used to allow for multiple comparisons and a *p*-value <0.01 considered as significant. In order to control the effect of potential confounding factors, the multiple linear regression analysis was applied.

Table 1. Duplex criteria for grading ICA stenosis.

Stenosis %	PSV	EDV	PSV_{ICA}/PSV_{CCA}
0–29	PSV $\leq$ 100	EDV<40	
30–49	100<PSV<130	EDV<40	
50–59	PSV>130	EDV<40	PSV ratio<3,2
60–69	PSV>130	40<EDV<110	3,2 $\leq$ PSV ratio<4
70–79	PSV>210	110<EDV<140	PSV ratio $\geq$ 4
80–95	PSV>210	EDV>140	PSV ratio $\geq$ 4
96–99		String flow	
100		Absence of flow	

PSV and EDV are in cm/s.

Results

Four hundred and forty-two carotid arteries were prospectively observed for a mean of 44 months (range: 12–120 months), leading to a total of 1620 arteries-years of follow-up. The average number of follow-up duplex scans was 7.3 $\pm$ 5.2 per patient (range: 2–20), while the total number of duplex scans that were performed was 3240. The overall mean rate of stenosis progression was 2.8% annually. However, significant progression of stenosis, resulting in a change of one or more spectral categories of carotid stenosis, occurred in 82 cases (19%). The mean annual incidence of disease progression was 5%. The mean progression rate in these cases was 15% annually (range: 5–50%). Two carotids progressed to total occlusion, both in male patients, one with uniformly echolucent and one with uniformly echogenic plaque. The first one progressed from 20% stenosis to total occlusion in 4 years' time and the second from 70% stenosis to total occlusion in 2 years. Both of them remained asymptomatic at the time of occlusion.

Patients with initial stenosis $\geq$50% had a 24% incidence of disease progression, while the incidence of disease progression in patients with initial stenosis <50% was 16%. Statistical analysis revealed that this difference was not significant ($p = 0.1$). Cumulative progression rate estimated by life-table analysis in both of these groups of patients is depicted in Fig. 1. As regards the patients' gender, progression of stenosis

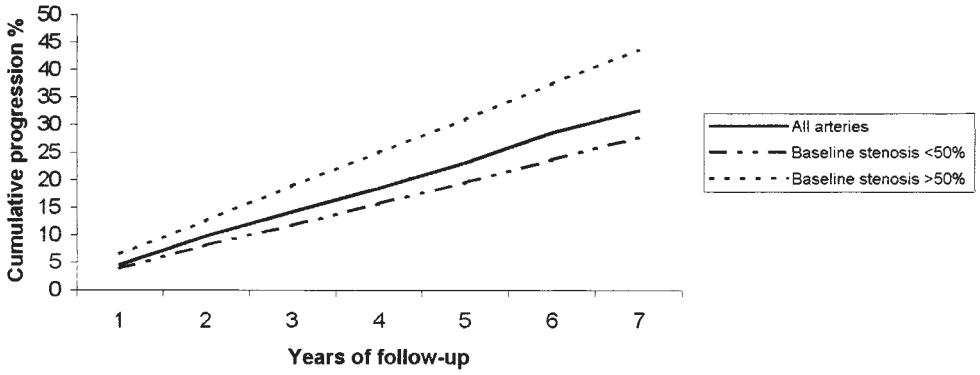

Fig. 1. Cumulative progression of carotid stenosis (% of patients progressing to a higher category) by life-table analysis.

Table 2. Association of incidence and annual rate of progression with gender.

Gender	Number of arteries	Incidence of progression (%)	*p*	Mean rate of progression	*p*
Males	320	19.4	0.9	3.24	0.041
Females	122	16.4		1.53	
Total	442	18.5		2.78	

Table 3. Association of incidence and annual rate of progression with age.

Age	Number of arteries	Incidence of progression (%)	*p*	Mean rate of progression	*p*
<65 years	189	20.2	0.4	2.88	0.8
≥65 years	253	16.4		2.64	
Total	442	18.5		2.78	

occurred in 19% of males and in 16% of females, a difference that was not statistically significant. Similarly, the rate of progression in males was 3%, while in females it was 1.5% ($p=0.041$), a difference that was not found to be statistically significant when the Bonferroni method was applied (Table 2). For the purpose of statistical correlation between age and stenosis progression, patients were divided into two groups: those younger and those older than 65 years (Table 3). Both groups had about the same incidence of disease progression (20% and 16% respectively, $p=0.4$). Age also did not seem to play a significant role in disease progression, when the rate of progression was taken into account (3% for both groups). As regards the clinical presentation of carotid stenosis, no statistically significant difference in the incidence of stenosis progression was recorded among the patients with history of TIAs (24%) or stroke (14%) and the asymptomatics (19%). The rate of progression among these groups of patients was also similar (Table 4).

Univariate statistical analysis revealed that there was no significant association between the occurrence of disease progression and coronary artery disease (CAD), diabetes mellitus (DM), hypertension, hypercholesterolaemia and smoking. Similarly, the rate of progression had no statistical correlation with any of these risk factors (Table 5). A statistically significant association was found between the ultrasonographic characteristics of the plaques and the incidence of progression (Table 6). Progression of stenosis occurred in 31.8% of uniformly echolucent plaques, while only in 16.9% of predominantly echolucent, in 17% of predominantly echogenic and in 16.8% of uniformly echogenic plaques ($p=0.03$). Progression of stenosis in the echolucent plaques was about four times faster than in the homogeneous, three times faster than in the

Table 4. Association of incidence and annual rate of progression with clinical presentation.

Clinical presentation	Number of arteries	Incidence of progression (%)	*p*	Mean rate of progression	*p*
Asymptomatic	290	18.6		2.41	
TIA	62	24.2	0.1	4.52	0.3
Stroke	90	14.4		2.78	
Total	442	18.5		2.78	

Table 5. Association of incidence and annual rate of progression with risk factors.

Risk factor	Number of arteries	Incidence of progression (%)	*p*	Mean rate of progression	*p*
CAD	145	22.8	0.3	4.10	0.1
DM	134	17.9	0.7	2.16	0.3
Hypertension	248	22.7	0.2	2.94	0.7
Hypercholesterolaemia	139	13.4	0.1	2.32	0.5
Smoking	370	19.7	0.8	3.07	0.8

Table 6. Association of incidence and annual rate of progression with the ultrasonographic characteristics of the plaque.

U/S characteristics of the plaque	Number of arteries	Incidence of progression (%)	*p*	Mean rate of progression	*p*
Echolucent	44	31.8		6.57	
Haemorrhagic	19	21.1		3.75	
Pred. echolucent	136	16.9	0.03	2.24	0.009
Pred. echogenic	146	17.0		1.53	
Echogenic	97	16.8		1.43	
Total	442	18.5		2.78	

predominantly echolucent and significantly faster than in the haemorrhagic plaques ($p=0.009$).

A multiple linear regression analysis was performed for all the variables having been submitted to statistical testing. The incidence or the rate of progression were defined as the dependent variables, while independent variables were the gender (1=Male, 2=Female), the age (continuous), the clinical presentation (ordered, 1=Asymptomatic, 2=TIA, 3=Stroke), the presence of CAD (1=No, 2=Yes), DM (1=No, 2=Yes), hypertension (1=No, 2=Yes), hypercholesterolaemia (1=No, 2=Yes), the smoking habit (1=No, 2=Yes) and the presence of uniformly echolucent (1=No, 2=Yes), haemorrhagic (1=No, 2=Yes), predominantly echolucent (1=No, 2=Yes), predominantly echogenic (1=No, 2=Yes), or uniformly echogenic carotid plaques (1=No, 2=Yes). The results of the regression analysis are shown in Tables 7 and 8. It can be seen that coronary artery disease and echolucent plaques were independently associated with the incidence and the rate of stenosis progression.

During the follow-up period, 387 (88%) of the arteries remained asymptomatic, 39 (9%) presented a TIA and 16 (4%) developed a stroke (Table 9). Neurological events occurred more frequently in patients with disease progression than in patients with stable lesions ($p<0.001$). Ninety-two carotid arteries were submitted to endarterectomy and 33 patients died of various causes during the 10-year follow-up. The indications for operation were the development of neurological symptomatology in 45 patients and the asymptomatic progression to stenosis >70% in 47 patients. Endarterectomy was performed in 47 out of the 56 patients who remained asymptomatic (since the other nine did

Table 7. Results from multiple linear regression analysis with the rate of progression as the dependent variable.

Variable	Coefficient	Std. Error	*t*	Sig.
Gender	−1.555	1.323	−1.175	0.241
Age	−0.012	0.038	−0.313	0.754
Symptoms	0.118	0.619	0.190	0.849
CAD	2.379	1.166	2.040	0.043
DM	−1.050	1.081	−0.971	0.333
Hypertension	0.619	1.079	0.574	0.567
Hypercholesterolaemia	−0.408	1.069	−0.381	0.703
Smoking	0.088	1.208	0.073	0.942
Echolucent plaques	5.580	1.827	3.054	0.003
Haemorrhage plaques	3.229	2.849	1.133	0.258
Pred. echolucent	−1.265	1.187	−1.066	0.288
Pred. echogenic	−1.407	1.218	−1.155	0.249
Echogenic	−1.464	1.200	−1.220	0.224

Table 8. Results from multiple linear regression analysis with the incidence of progression as the dependent variable.

Variable	Coefficient	Std. Error	*t*	Sig.
Gender	−0.069	0.072	−0.965	0.336
Age	−0.003	0.002	−1.692	0.092
Symptoms	−0.033	0.033	−0.988	0.324
CAD	0.147	0.063	2.329	0.021
DM	−0.041	0.058	−0.705	0.482
Hypertension	0.083	0.058	1.422	0.156
Hypercholesterolaemia	−0.080	0.058	−1.376	0.170
Smoking	−0.006	0.065	−0.092	0.927
Echolucent plaques	0.231	0.099	2.337	0.020
Haemorrhagic plaques	0.155	0.154	1.006	0.316
Pred. echolucent	−0.088	0.085	−1.043	0.298
Pred. echogenic	−0.077	0.066	−1.169	0.244
Echogenic	−0.081	0.065	−1.241	0.216

Table 9. Association between progression of stenosis and clinical outcome.

Clinical outcome	Total	Progressors	Non-progressors	*p*
Asymptomatic	387 (87.6%)	56 (68.3%)	331 (92%)	
TIA	39 (8.8%)	17 (20.7%)	22 (6.1%)	<0.001
Stroke	16 (3.6%)	9 (11%)	7 (1.9%)	
Total	442	82	360	

not progress to >70% stenosis), in five out of the nine patients who developed stroke (since the other four had disabling or fatal strokes) and in all of the 17 patients who presented TIAs. Among the patients with stable lesions, endarterectomy was performed in 19 out of the 22 patients who developed TIAs (since the other three had stenosis <50%) and in four out of the seven patients who presented with stroke (since the other two had disabling injuries and one patient a low-degree stenosis).

Coronary artery disease was the leading cause of death in our patients, accounting for 25 (76%) deaths. Three patients (9%) died of cancer, two patients (6%) had fatal strokes, while the other three (9%) patients died of miscellaneous causes.

Discussion

The reported incidence of carotid artery stenosis progression ranges from 4% to 29%.[4–13] However, these results are somewhat inconsistent, considering the

differences among the various studies in the definition of carotid artery disease progression and the duration of follow-up. Most authors define stenosis progression as any change in carotid stenosis to a higher spectral category[9–12] and some as an increase above an arbitrarily set limit ranging from 50% to 80%.[4–8] As regards the duration of follow-up, results would be comparable only if they were expressed in annual rates. In several large series the estimated annual incidence of disease progression ranged from 1.5% to 7%.[4–13] Our 5% incidence of ICA stenosis progression is in accordance with these studies.

Several risk factors have been studied in order to identify groups of patients being at higher risk for disease progression. Young[9] or old[5,14] age, degree of initial stenosis,[5,9] smoking,[14] low levels of HDL,[9] high levels of Ip(a)[9] and LDL,[14] high blood pressure,[6] low ankle–brachial index[6] and high PSV[6] have been implicated in ICA stenosis progression. Nevertheless, other studies have failed to document any association between progression of stenosis and age,[6] sex,[5,6,12] diabetes mellitus,[5,6,12] smoking,[5,6,12] coronary artery disease,[5,6,12] hypercholesterolaemia[6] or initial clinical presentation.[6,12] In accordance with these studies, no statistically significant correlation was found between the above-mentioned factors and disease progression in our series, except for CAD, which was found to be associated with a higher incidence of stenosis progression. Disease progression was also significantly associated with the ultrasonographic characteristics of the plaques. Uniformly echolucent plaques (type I) showed a higher incidence of stenosis progression (32%) compared with other types of plaques. These results are in contrast with the findings of Iafrati *et al.*[5] who did not find plaque morphology to play a significant role in disease progression. Previous studies have found an association between plaque haemorrhage and high-grade stenosis, though the cause-and-effect relation between these two factors remains unclear.[15–17] In our study, haemorrhagic plaques did not show a higher incidence of disease progression comparing with other types of plaques. Thus, it seems that high-grade stenosis is the cause and plaque haemorrhage the effect and not vice versa.

Except for the annual incidence of carotid artery stenosis progression, it would be important to know the annual rate of progression, indicating how fast the lesion is progressing. Up to now, all published series give information only on the incidence of progression. In our series the overall mean rate of stenosis progression was 3% annually. When only carotid arteries with disease progression were taken into account, progression rate was 15% annually (range 5–50%). Statistical analysis revealed no significant association between the rate of progression and any of the risk factors studied in our series, except for CAD and ultrasonographic characteristics of the plaque. Patients with CAD and patients with uniformly echolucent plaques presented higher rate of stenosis progression (4 and 7%, respectively). The results of our study show that the diagnostic yield of carotid ultrasonography in patients with asymptomatic stenosis of any degree or symptomatic stenosis <50% is too low to justify a formal follow-up programme in these patients. However, by confining such a surveillance programme only to groups of patients being at greater risk for stenosis progression or by varying the intensity of duplex surveillance based on the existing risk factors, the cost-to-benefit ratio can be improved.

In conclusion, our findings suggest that patients with CAD as well as those with uniformly echolucent plaques on initial examination are in need of close monitoring by ultrasonography, in order to detect progressive lesions which may require end-arterectomy.

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